

# Congenital rubella syndrome: ophthalmic manifestations and associated systemic disorders

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## Abstract

**Congenital rubella syndrome has a wide variety of severe ophthalmic and systemic complications. A worldwide rubella epidemic from 1963 to 1965 affected thousands of infants. This is a 20 year follow up study of patients with congenital rubella syndrome analysing the prevalence of ophthalmic disorders, associated systemic problems, and correlations among these defects. The authors statistically analysed 125 cases of congenital rubella seen in the Mayo clinic ophthalmology department over a 32 year interval. Most patients were young adults. Ocular disease was the most commonly noted disorder (78%), followed by sensorineural hearing deficits (66%), psychomotor retardation (62%), cardiac abnormalities (58%), and mental retardation (42%). Multiorgan disease was typical (88%). Ocular disease and hearing loss were frequently associated (53% had both) but not significantly correlated. A similar association existed between ocular and cardiac disease. Cataracts and microphthalmia were significantly correlated with poor visual acuity (each  $p < 0.0001$ ). Glaucoma was significantly correlated with cataracts ( $p = 0.0002$ ) and microphthalmia ( $p = 0.0024$ ) but not poor visual acuity. Four patients with microphthalmia developed late onset glaucoma. No significant association was found between gestational age at time of maternal infection and the incidence of individual ocular conditions. However, several cardiac disorders were significantly associated with gestational age. Although new cases of congenital rubella are rare, surviving victims continue to challenge the ophthalmic and medical communities with a wide range of ocular and systemic disorders.**

(*Br J Ophthalmol* 1993; 77: 358-363)

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Accepted for publication  
2 February 1993

Veale, a Scottish physician, characterised rubella as a benign contagious disease in 1866.<sup>1</sup> A century later, Sir Norman Gregg described the triad of congenital cataracts, deafness, and heart defects in children of women who had contracted the infection during the first trimester.<sup>2,3</sup> The tremendous morbidity associated with the congenital rubella syndrome is now well known to the medical community.

Before perfection of an effective vaccine in 1969, a worldwide rubella epidemic lasting from 1963 to 1965 affected an estimated 10% of pregnant women; approximately 30% of infants from infected mothers ultimately manifested congenital disease.<sup>4</sup> One recent estimate suggests that, in the United States alone, at least 10 000 infants were born with moderate to severe manifestations during that epidemic.<sup>5</sup> Over the course

of the ensuing 20 years, many of those infants have matured into young adults who pose an enormous challenge to the medical community. The complexity and multiplicity of their defects demand the combined disciplines of medicine, special education, and rehabilitation. Because serious ocular abnormalities are commonly associated with congenital rubella, ophthalmologists share the responsibility of managing these patients.

Epidemiological assessment of ocular disease in large populations of congenital rubella patients are few; 17 years have passed since Wolff, following a cohort of victims from the 1963-65 epidemic, published the last indepth report.<sup>6</sup> Many of the earlier studies employ only descriptive statistics, commenting on apparent associations without actually testing their validity. The subject is worthy of continuing attention, especially because additional ocular disorders associated with congenital rubella have been characterised since Wolff's paper, and because some defects may continue to evolve many years after birth.<sup>7-9</sup> We reviewed retrospectively 125 congenital rubella cases to discern the prevalence of specific ocular defects, identify associated systemic abnormalities, and discern statistical correlations (if any) among these defects.

## Materials and methods

Charts of all patients with a diagnosis of congenital rubella seen in the Mayo clinic's department of ophthalmology from 1950 to 1982 were reviewed. Criteria for diagnosis of congenital rubella syndrome included classic stigmata (cardiac anomalies, hearing defects, cataracts), plus a history of maternal exposure coupled with rash or positive immunoglobulin M serology and/or isolation of the virus.

Primary demographic data included sex, race, date of birth, date of diagnosis, estimated gestational age at the time of maternal infection, residence (Olmstead County, MN, versus all other locations), and the data and patient status at last follow up examination. Records were screened for many clinical variables, tallied in Table 1 (ophthalmic involvement) and Table 2 (involvement of non-ocular systems).

To elucidate correlations among the most prevalent ocular findings (pigmentary retinopathy, cataract, microphthalmia, glaucoma), a battery of statistical tests was applied to the data, examining the coincidence of these conditions with all other ocular findings. In a separate analysis gestational age at time of maternal rubella infection was compared with the incidence of the most common ocular and systemic disorders. All testing was performed using SAS

**Table 1** Manifestations of ocular disease among 125 patients with the congenital rubella syndrome

Symptom	Unilateral		Bilateral		Total (%)	Others (%)*
	No	%	No	%		
Retinopathy	4	3	71	57	60	9-61 <sup>15 26</sup>
Cataracts	13	10	21	17	27	16-85 <sup>6 21</sup>
Strabismus	—	—	30	24	24	9-60 <sup>21 24</sup>
Nystagmus	5	4	26	21	25	13-38 <sup>6 15</sup>
Microphthalmia	19	15	10	8	23	10-63 <sup>6 21</sup>
Amblyopia	12	10	8	6	16	1 <sup>6</sup>
Glaucoma	6	5	5	4	9	2-25 <sup>14</sup>
Iris coloboma	4	3	2	2	5	1 <sup>15</sup>
Optic atrophy	2	2	2	2	4	9 <sup>6</sup>
Corneal haze	3	2	1	1	3	1-8 <sup>6 15</sup>
Dacryostenosis	3	2	—	—	2	4 <sup>15</sup>
Any eye disease	—	—	—	—	78	30-68 <sup>12 14</sup>

\*Figures published by other authors.

**Table 2** Systemic manifestations of congenital rubella

Symptom	No	%
Otological		
Sensorineural defects	82	66
Unilateral	1	1
Bilateral	81	65
Degree of hearing loss		
Mild	3	3*
Moderate	23	19*
Severe	55	44*
Cardiac		
Patent ductus arteriosus	41	33
Pulmonary stenosis	32	26
Ventricular septal defect	21	17
Tetralogy of Fallot	3	2
Coarctation of aorta	1	1
Mitral stenosis	2	2
Atrial septal defect	6	5
Developmental		
Failure to thrive		
Mild	40	32
Moderate	34	27
Severe	1	1
Psychomotor retardation		
Mild	27	22
Moderate	38	30
Severe	12	10
Mental retardation		
Mild	23	18
Moderate	14	11
Severe	15	12
Low birth weight (<2500 grams)	58	46
Prematurity (<36 weeks)	32	26
Neurological		
Microcephaly	53	42
Hyperactivity	22	18
Spastic diplegia	18	14
Seizure disorder	9	7
Spastic quadriplegia	2	2
Hydrocephalus	2	2
Hemiparesis	1	1
Other diagnoses	6	5
Genitourinary		
Inguinal hernia		
Unilateral	7	10
Bilateral	2	3
Recurrent urinary tract infections	7	10
Undescended testes		
Unilateral	14	20
Bilateral	3	4
Hydrocele		
Unilateral	2	3
Bilateral	1	1
Hypospadias	2	3
Meatal stenosis	3	4
Hydronephrosis	1	1
Urinary reflux	2	3
Orthopaedic		
Syndactyly	3	4
Scoliosis	3	4
Dislocated hip	2	3
Legg-Perthes disease	2	3
Peroneal palsy	1	1
Calcaneovalgus deformity	1	1
Dental		
Micrognathia	6	9
Hypoplastic teeth	3	4
Cleft lip	2	3
Endocrine		
Diabetes mellitus	3	4
Graves' disease	2	3
Hashimoto's thyroiditis	2	3

\*Audiometric data were available for only 103 patients; these percentages reflect that total.

software (SAS Institute Inc, SAS Campus Drive, Cary, NC 27513, USA) on a VAX mainframe computer. Analyses included  $\chi^2$ , Wilcoxon two sample, and Fisher's exact tests. Probability values of  $p < 0.05$  were considered statistically significant.

## Results

One hundred and twenty five patients fulfilled the diagnostic criteria for the congenital rubella syndrome. Sex distribution was approximately equal, with 71 men and 54 women affected (57 and 43%, respectively). One hundred and fourteen patients (93%) were still alive at the last date of follow up. All but three of the patients were white; no black patients were among the study population. The median gestational age at the time of maternal infection was 8 weeks (range, 0 to 29 weeks). The majority of patients (51%) were born during the worldwide rubella epidemic from 1963 to 1965 (Fig 1).

Age at diagnosis for patients residing in Olmstead County ranged from 0 to 270 days, 45 days being the mean. In contrast, the mean age at diagnosis of all 125 patients was 4.6 years. This delay reflects the high proportion of patients who were tertiary referrals. Only eight of the 125 patients were residents of Olmstead County; of those eight, 50% had ocular disease, compared with 80% of the non-residents (difference not statistically significant:  $p = 0.074$ , Fisher exact test; power of test to detect significant difference = 51%). The mean duration of follow up was 4.5 years with ages ranging from less than 1 year to 65 years (Fig 2).

Ocular disorders in the study group are listed in Table 1. Overall, 78% of the group (97 patients) had some form of ocular disease. The most common finding was pigmentary retinopathy, seen in 75 patients (60%) and usually present in both eyes (71 out of 75). Cataracts followed retinopathy in frequency (34 patients or 27%). Sixty per cent of the latter group (21 patients) had bilateral involvement. Glaucoma was noted in 11 patients (9%). No cases of subretinal neovascular membranes, chronic inflammation, progressive cataracts, spontaneous resorption of cataracts, or congenital aphakia were detected.

No significant relationships were detected between pigmentary retinopathy and any other defect, including visual acuity; however, because of limited subgroup sample sizes, the power of our analyses to detect a statistically significant relationship was typically very low for most of the comparisons. For instance, the power to discern a relationship between poor visual acuity (defined as worse than 20/200) for data collected from right and left eyes was only 5% and 15%, respectively. However, statistically significant associations involving other ocular diseases were identified (Table 3). Notably, the incidence of cataracts in microphthalmic eyes was almost 90% ( $p < 0.0001$ ), and both of the latter conditions were significantly correlated with poor visual acuity, regardless of prior ophthalmic surgeries ( $p < 0.0001$ ). Among aphakic patients, acuity ranged from 20/70 to no light perception, mean acuity at last follow up visit being 10/200.

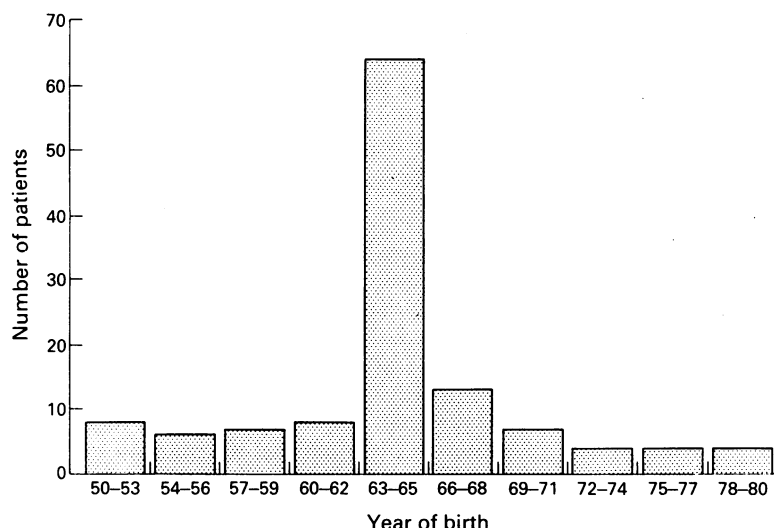


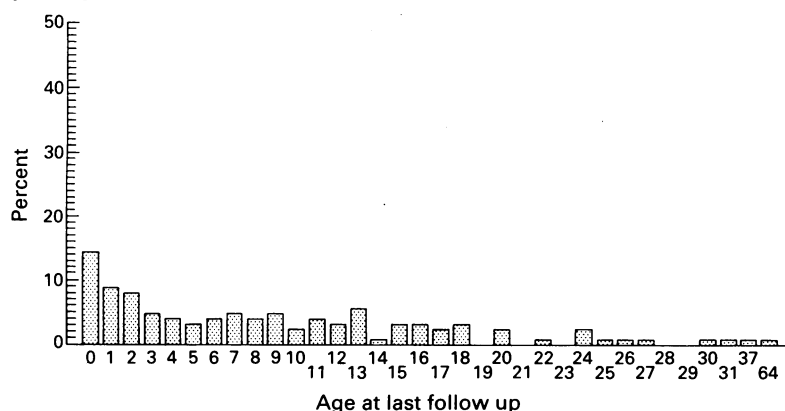
Figure 1 Breakdown of study population by year of birth.

Glaucoma was significantly correlated with microphthalmia ( $p < 0.0024$ , Fisher's exact test). Ten of the 11 patients with glaucoma also had cataracts. Four patients developed glaucoma in their late teens. Two of the latter cases involved previously unoperated microphthalmic eyes, and two involved aphakic, microphthalmic eyes. Patients requiring glaucoma surgery typically required repeat glaucoma operations as well. In most cases, the primary surgical procedure was goniotomy.

Involvement of non-ocular systems is detailed in Table 2. Hearing loss was common in this patient population. Moreover, the prevalence of hearing loss in the entire study group (66%) was similar to the prevalence of hearing loss in the eye disease subgroup (53%). Similarly, the occurrence of eye disease in the entire study group (78%) was comparable to that among hearing-impaired patients (80%). Although the frequent association between ocular disease and hearing deficits was not statistically significant ( $p = 0.28$ ,  $\chi^2$  test), the power of the test to detect such a difference was only 18%.

Cardiac defects and ocular disease were also frequently associated in this population (60 patients, or 48%, had both). The prevalence of cardiac disease among patients with eye disease was 62%, compared to 58% for the entire study group. Conversely, the prevalence of eye disease among patients with heart disease (82%) was similar to that for the entire population (78%). This relationship was not statistically significant

Figure 2 Distribution of the ages of the study population at the time of last follow up visit.



( $p = 0.145$ ,  $\chi^2$  test); the power of the test to detect such a difference was 31%.

The preponderance of defects in the study population occurred in infants exposed to rubella during the first trimester of gestation. While the prevalence of hearing deficits tended to increase with time of maternal rubella infection during the first trimester, the prevalence of ocular and cardiac disease went down (Fig 3); however, only the cardiac trend was statistically significant ( $p = 0.009$ , Wilcoxon rank sum test); the trend for hearing defects was of borderline significance ( $p = 0.086$ , Wilcoxon rank sum test). Although the correlation between gestational age and any single ocular condition was statistically not significant, significant associations were found between gestational age and the following specific cardiac diseases: patent ductus arteriosus, pulmonary stenosis, ventricular septal defect, and failure to thrive (Table 3).

A large proportion of the patients demonstrated some degree of developmental or intellectual deficiency. Sixty two per cent of the patients had a history of psychomotor retardation, and 42% had microcephaly. Table 2 lists the prevalence of other systemic manifestations of congenital rubella, including genitourinary, orthopaedic, dental, and endocrine problems.

Overall, multiorgan disease was the rule: 88% of the patients suffered involvement of at least two systems, and nearly two thirds (64%) had abnormalities in four or more systems. Only one patient with the diagnosis of congenital rubella had no detectable defects on last examination.

## Discussion

The classic rubella syndrome is characterised by the combination of cardiac, ocular, and hearing defects, although infection and damage can occur in every organ system. As many as two thirds of infants with congenital rubella will be free of any abnormality at birth. Most patients who are symptomatic at birth and many of those who lack signs of infections eventually will have some degree of hearing loss or psychomotor damage. Congenital rubella should be viewed as a chronic infection capable of producing progressive damage. Clinical follow up and testing have shown that ultimately central nervous system damage (hearing loss, intellectual and motor deficiencies) is the most frequent and significant clinical problem associated with congenital rubella. The diagnosis should be suspected when maternal seroconversion or a compatible illness occurs during pregnancy, when a neonate has clinical signs of congenital rubella, and in any infant with hearing loss, retinitis, or encephalopathy of unknown aetiology. Even with a high index of suspicion, many cases will be missed, since many mothers and infected newborns also lack clinical signs of rubella.<sup>10</sup>

Both the rate of in utero transmission of rubella and the consequences of fetal infection are related to the stage of gestation at the time of maternal infection. Infection during the first 8 weeks of pregnancy results in a fetal infection rate of about 50%; subsequently, the rate of in utero transmission drops sharply to less than 10% by the 16th week. The proportion of

Table 3 Significant correlations among 125 patients with the congenital rubella syndrome

Correlative symptom	Poor visual acuity	Cataracts	Glaucoma	Gestational age
Cataracts	p<0.0001*	—	—	—
Microphthalmia	p<0.0001*	p<0.0001*	p<0.0024†	—
Glaucoma	—	p<0.0002*	—	—
Patent ductus arteriosus	—	—	—	p<0.0158‡
Pulmonary stenosis	—	—	—	p<0.0359‡
Ventricular septal defect	—	—	—	p<0.0294‡
Failure to thrive	—	—	—	p<0.419‡

\* $\chi^2$  test; †Fisher exact test; ‡Wilcoxon two sample test.

infected fetuses with damage caused by rubella follows a similar pattern. These gestational influences probably are due to a number of factors, including timing in relation to organogenesis, maturation of fetal host mechanisms, and maturation of the placental barrier. Developing fetal organs are damaged by infection of cells in blood vessels in both the placenta and fetus. These vascular lesions are characterised by endothelial necrosis and are often accompanied by petechiae and haemosiderin laden macrophages in fetal organs. In addition, rubella can produce cytolytic infection of host cells; cellular damage caused by virus has been identified in a number of tissues, including myocardium, central nervous system, skeletal muscle, and epithelial cells of the developing inner ear, lens, and teeth.<sup>10</sup>

In the 1960s and '70s, publications concerning congenital rubella were legion. Since the advent of effective vaccination, the number of new cases of congenital rubella has plummeted and with it the number of reports addressing this devastating disease. Nonetheless, congenital rubella continues to have a sizeable impact on the medical and social community: conservative estimates place society's cost for the long term rehabilitation of patients from the 1963–65 epidemic at \$US1–3 billion.<sup>11</sup> Because eye disease accounts for much of this burden, congenital rubella merits continued attention from the ophthalmic community.

Most papers from the ophthalmic literature regarding this disease report the incidence and coincidence of various eye findings without test-

ing the data statistically. Arguably, in many earlier reports such analysis was problematic, owing to very small samples, uncontrolled variables, and non-random patient populations. While the current study suffers from the usual limitations of a retrospective approach, we none the less feel that prudent application of selected statistics may help clarify important relationships and stimulate directions for further study.

The present study has certain advantages over previous reports: a larger sample size than most, a broader range of patient ages, longer follow up, and more complete assessment of concomitant ocular and systemic variables. On the other hand, our population is heavily skewed towards patients with ocular disease. Because the Mayo clinic is a tertiary referral centre situated in a relatively small city, the majority of patients in this study were probably screened elsewhere and referred specifically because of known eye problems. Not surprisingly, the overall prevalence of ocular disease in this population, 78%, is higher than the 43% prevalence of eye disease described by Wolff in his prospective review of infants with congenital rubella (of the 11 different eye conditions that Wolff documented in his study, all but two were more frequent among our patients).<sup>6</sup> Notably, the present study documented a higher overall frequency of ocular disorders, even when compared with other retrospective series (a literature search showed a high of 68%).<sup>12</sup> Longer follow up and larger sample size are probable factors, as both favour discovery of rarer, overlooked, or delayed eye conditions (for example, delayed glaucoma).

Several authors have commented on the frequent association of hearing deficits and ocular disease in congenital rubella patients. Woodruff, in her study of children attending a school for the deaf, noted that 82% of congenital rubella patients with ocular findings were hearing impaired.<sup>13</sup> This figure parallels the 80% prevalence of ocular disease among hearing impaired patients in our study. Some authors have implied that the association between these two defects is non-random.<sup>14</sup>  $\chi^2$  analysis of our data suggests the association of these common findings is only coincidental. An alternative explanation is that this test had insufficient power (only 18%) to uncover a significant relationship, given the limitations of our data. If the ocular and otic systems share some embryological feature resulting in similar vulnerability to rubella dysgenesis, the current evidence remains circumstantial.

Cardiac anomalies are one component of Gregg's archetypal rubella syndrome. Subsequent authors have commented on the specific association between ocular and cardiac defects in these patients.<sup>15,16</sup> Seltzer *et al* reported, for instance, that of a population of 100 congenital rubella patients, 95% of the subgroup with eye disease had associated cardiac defects, compared with only 56% of the group without eye disease.<sup>15</sup> Our data show a much lower prevalence of cardiac defects (62% in patients with eye findings) and approximately the same frequency of cardiac defects among patients with ocular disorders as among the entire study population. As with the analysis of hearing deficits and ocular disease, however, the power of the  $\chi^2$  test to

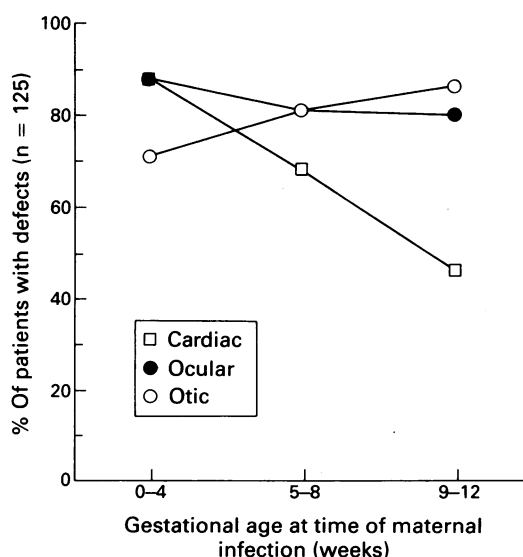


Figure 3 Prevalence of selected organ defects relative to gestational age at the time of maternal rubella infection.

identify a significant relationship was significantly lessened by sample size.

Several previous studies have described the apparent rarity of combined glaucoma and cataracts in congenital rubella patients,<sup>14-17-19</sup> implying that these conditions are mutually exclusive. Wolff<sup>5</sup> questioned this conclusion, and with  $\chi^2$  analysis of prospective patient data showed that the infrequency of the association was due to the overall rarity of glaucoma in all rubella patients, including those with cataracts; glaucoma and cataracts behaved like independent events, and the chance of a patient having both conditions was correspondingly much less than that of having only one. In contrast, our analysis suggests that the two conditions occur together significantly more often than by chance alone. Because glaucoma among congenital rubella patients is not a homogeneous disease, however, such analysis is complicated. The delayed glaucoma following cataract surgery (seen in two of our patients) is felt to have a pathophysiology different from the infantile glaucoma more commonly associated with the rubella syndrome.<sup>20</sup>

Microphthalmia is another variable that may influence rubella related glaucoma. Wolff<sup>5</sup> observed that glaucoma in congenital rubella patients 'may have a special predilection for microphthalmic eyes that have undergone cataract surgery, sometimes years earlier'. In our patient population, microphthalmos was highly correlated with glaucoma, irrespective of previous surgery. Cataracts also showed a very statistically significant relationship with both microphthalmia and glaucoma in our population. While proteins leaking from hypermature cataracts may promote elevated intraocular pressure (for example, as in phacolytic glaucoma), our data do not clarify whether the glaucoma in microphthalmic eyes is secondary to lens mediated effects, angle abnormalities, or both.

The association between microphthalmos and cataracts, though frequent, is not well understood. In our study, almost 90% of the microphthalmic eyes had cataracts; similarly, O'Neill reported that 100% of 12 culture proved congenital rubella patients with microphthalmia had cataracts.<sup>21</sup> In contrast, other researchers have reported microphthalmos as 'usually, but not necessarily' linked with cataract.<sup>22</sup>

Some authors feel that microphthalmos is a non-specific consequence of congenital rubella, a sort of ocular failure to thrive,<sup>5</sup> perhaps due to the generalised slowing of replication commonly seen in rubella infected cells.<sup>23</sup> Microphthalmos may, therefore, signify diffuse ocular involvement with virus, although this has not been substantiated in vitro. That an eye with more rubella damaged cells might have several simultaneous defects – that is, glaucoma and cataracts, seems plausible.

While most published reports agree that defects from congenital rubella are more profound and numerous when maternal infection occurs in the first trimester, even third trimester infection may result in significant disease. The literature disagrees, however, as to the exact timing of specific embryological insults. For instance, one author felt the risk of cataract sharply declined after week 5 of gestation, when

the embryologic lens capsule was complete<sup>17</sup>; Wolff,<sup>5</sup> however, wrote that the period of vulnerability extends to week 11. Cooper and Krugman<sup>16</sup> felt that hearing deficits resulted primarily from material infection occurring after the eighth week of gestation; Boniuk,<sup>24</sup> however, attributed hearing deficits to infections preceding the eighth week. Our data did not demonstrate any statistically significant trends between individual ocular diseases and gestational age. Determining precise gestational age at the time of maternal infection is inherently difficult, however, and this factor may have weakened the analysis. Conversely, several cardiac defects demonstrated strong associations with gestational age at time of maternal infection, perhaps reflecting a more sharply defined period of embryonal vulnerability for this organ system.

Delayed ocular disease is an increasingly important consideration in patients with congenital rubella. The characteristic 'salt-and-pepper' pigmentary retinopathy shows progressive tendencies in some patients,<sup>25</sup> although early reports implied the condition was stationary.<sup>26</sup> Patients with retinopathy may enjoy relatively good visual acuity into adulthood, then experience sudden loss of vision secondary to subretinal neovascularisation.<sup>7,27,28</sup> Even without identifiable neovascularisation, visual acuity may occasionally reach no more than 20/60 in patients whose only ocular finding is pigmentary retinopathy.<sup>5</sup> Of 27 patients in our series with isolated retinopathy, one had vision in the 20/100–20/200 range in one eye; interestingly, the vision in the fellow eye was in the 20/20–20/30 range.

Diabetic retinopathy is considered an increasing threat in congenital rubella patients, since many develop diabetes mellitus with age. Twenty per cent of Gregg's 1941 study cohort had developed clinical diabetes at last follow up; diabetic retinopathy appeared in one patient by the age of 18 months.<sup>29</sup> Although three patients in the present study had documented diabetes, no diabetic retinopathy was observed.

Like the studies before it, the present review underlines the multiplicity and severity of defects in the congenital rubella syndrome. However uncommon the disease has become, it remains a serious and sometimes treatable threat to vision in thousands of patients.

This paper was presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Sarasota, May 1990. Supported in part by NIH Grants EY07701 and EY00331, and the Lucille Ellis Simon Glaucoma Research Fund, Los Angeles, CA, USA.

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